Synthesis of the Isomeric Mono- and Bisoxiranylpyrenes

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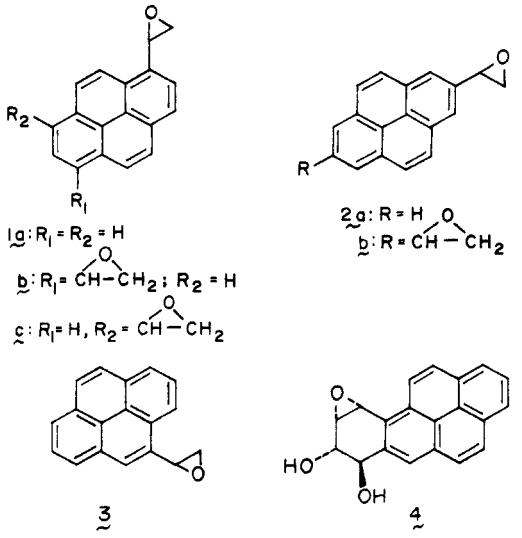
1-Oxiranylpyrene (**1a**) exhibits potent mutagenic activity in both bacterial[2] and mammalian[3] cells, efficiently inhibits replication of ϕX 174 viral DNA,[4] and binds covalently to SV 40 DNA, causing unwinding of the supercoiled DNA helix.[2,5] 1-Oxiranylpyrene is also a close structural analogue of *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**4**) implicated as the ultimate carcinogenic metabolite of benzo[*a*]pyrene.[5] In view of these properties of **1a**, it was of interest to test the bioactivity of its two isomers, 2- and 4-oxiranylpyrene (**2a** and **3**), as well as the bisoxiranyl derivatives of pyrene. The latter are potential nucleic acid cross-linking agents

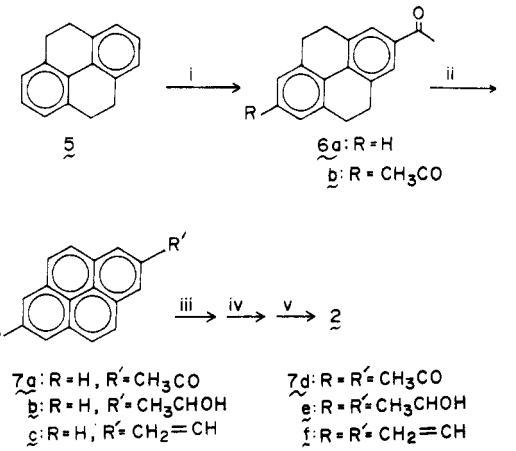


We now report synthesis of the previously unknown 2- and 4-oxiranylpyrenes (**2a** and **3**) as well as the three bisoxiranyl derivatives 1,6-, 1,8-, and 2,7-bisoxiranylpyrene (**1b**, **1c**, and **2b**).

Results and Discussion

Two synthetic approaches to the monooxiranylpyrenes were investigated: (a) Corey reaction of the corresponding pyrene aldehydes with dimethylsulfonium methylide[6] and (b) epoxidation of the related vinyl derivatives of pyrene. The former method was employed in the previously reported synthesis of 1-oxiranylpyrene.[7,8]

Scheme I[a]



[a] i = CH_3COCl, $AlCl_3$; ii = DDQ; iii = $NaBH_4$; iv = H^+; v = *m*-chloroperbenzoic acid.

Synthesis of 4-oxiranylpyrene (**3**) was accomplished by the Corey method from pyrene-4-carboxaldehyde. The latter was itself synthesized from 4-bromopyrene by transmetalation with *n*-butyllithium to generate 4-lithiopyrene, followed by reaction with dimethylformamide. An inherent problem in dealing with these relatively reactive aryl epoxides is their tendency to decompose during attempted purification by conventional methods. Efficient purification of **3** was achieved by passage through a column of neutral alumina, activity IV, eluted with 4% dioxane in cyclohexane, and trituration with pentane. Pure **3**, mp 88–89 °C, was obtained in 90% yield by this method. Use of this procedure to purify 1-oxiranylpyrene, synthesized as previously described,[7,8] afforded an improved yield of pure **1a**.

Synthesis of 2-oxiranylpyrene (**2a**) posed a more difficult challenge in that introduction of substituents into the 2-position of pyrene cannot be achieved directly. Since 4,5,9,10-tetrahydropyrene (**5**) is known to undergo substitution in this site,[9] it provides a convenient starting compound. When initial attempts to prepare pyrene-2-carboxaldehyde through Vilsmeier reaction of **5** were unsuccessful, we undertook the preparation of **2a** from **5** via the sequence in Scheme I. Hydrogenation of 4,5-dihydropyrene over the K-region-specific catalyst palladium[10] afforded **5** essentially quantitatively. Friedel–Crafts reaction of **5** with $AlCl_3$ and acetyl chloride in carbon disulfide afforded smoothly the product of monosubstitution, 2-acetyl-4,5,9,10-tetrahydropyrene (**6a**). Dehydrogenation of **6a** with DDQ gave 2-acetylpyrene (**7a**). Reduction of the latter with $NaBH_4$ followed by dehydration with *p*-toluenesulfonic acid provided 2-vinylpyrene (**7c**). Epoxidation of **7c** with *m*-chloroperbenzoic acid furnished 2-oxiranylpyrene.

Synthesis of 2,7-bisoxiranylpyrene (**2b**) was readily accomplished via an analogous sequence from 2,7-diacetyl-4,5,9,10-tetrahydropyrene (**6b**). The latter was conveniently synthesized in excellent yield (98%) through Friedel–Crafts acetylation of **5** with acetyl chloride and $AlCl_3$ in CH_2Cl_2 in place of CS_2 employed in the preparation of **6a**.

Attempted synthesis of 1,6- and 1,8-bisoxiranylpyrene (**1b**, **1c**) through epoxidation of 1,6- and 1,8-bisvinylpyrene were frustrated by the facility of polymerization of these

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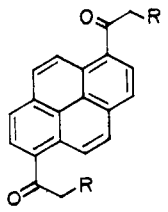
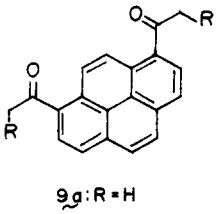
olefins. Therefore, an alternative synthetic approach involving reductive cyclization of 1,6- and 1,8-bis(bromoacetyl)pyrene (**8b** and **9b**) was explored.[11] The bromo ketones **8b** and **9b** were obtained through bromination of 1,6- and 1,8-diacetylpyrene (**8a** and **9a**) with $CuBr_2$. Reduction of **8b** and **9b** with $NaBH_4$ furnished smoothly in good yields the corresponding bisoxiranyl compounds **1b** and **1c** as crystalline solids.



8a: R = H
b: R = Br



9a: R = H
b: R = Br

The NMR spectra of all products and intermediates were entirely consistent with their structural assignments. In particular, the oxiranyl derivatives all exhibited a characteristic oxiranyl NMR spectral pattern closely resembling that of 1-oxiranylpyrene[7,8] (cf. Experimental Section).

According to the bay region theory,[12] which has been employed with moderate success to predict the mutagenic and tumorigenic activities of epoxide derivatives of polycyclic hydrocarbons, these activities are directly related to SN_1 reactivity as predicted by the differences in delocalization energies ($\Delta E_{deloc}/\beta$) of the zwitterionic intermediates bearing a positive charge on the benzylic carbon atom. $\Delta E_{deloc}/\beta$ of **1a**, **2a**, and **3** calculated by the perturbational MO method[12] are 0.794, 0.488, and 0.714, respectively. Biological studies on the mono- and bisoxiranylpyrenes to test these predictions are currently in progress and will be reported separately.

Experimental Section

General Methods. The NMR spectra were obtained on a Varian EM 360 spectrometer or The University of Chicago 500-MHz NMR spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Integration was consistent with all structural assignments. Melting points are uncorrected. All new compounds gave satisfactory microanalysis for C, H within ±0.3% and/or mass spectra consistent with the assigned structures.

Materials. Pyrene-1-carboxyaldehyde [mp 128–128.5 °C (lit.[13] mp 126 °C)] was synthesized in 75% yield by the method of Vollmann et al.[13] 4-Bromopyrene was obtained as described previously by Konieczny and Harvey.[14] 4,5-Dihydropyrene was prepared by lithium–ammonia reduction of pyrene.[15] 4,5,9,10-Tetrahydropyrene (mp 126–127 °C) was obtained essentially quantitatively through hydrogenation of 4,5-dihydropyrene (2.04 g, 10 mmol) in ethyl acetate (20 mL) over a 10% Pd on charcoal catalyst (500 mg) at 50–55 psig for 72 h by the general method of Fu et al.[10] 1,6- and 1,8-diacetylpyrene were prepared by acetylation of pyrene with acetyl chloride and $AlCl_3$ in CS_2 as described.[16] *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.5 phosphate buffer and drying under reduced pressure.

Ether was dried over sodium. Benzene was distilled from calcium hydride and stored over molecular sieves. Tetrahydrofuran (THF) was freshly distilled, first from lithium metal, then from $LiAlH_4$. Dimethylformamide (DMF) and dimethyl sulfoxide (Me_2SO) were stored over molecular sieves. *n*-Butyllithium (1.6 M in hexane) was purchased from the Aldrich Chemical Co.

1-Oxiranylpyrene (1a). This compound was synthesized through reaction of pyrene-1-carboxaldehyde (2.0 g, 8.7 mmol) with dimethylsulfonium methylide generated from trimethylsulfonium iodide with NaH by the general procedure of Corey;[6] NaH was more convenient than *n*-butyllithium empoloyed in our earlier procedure.[7] A similar method was described by Yang and co-workers.[8] The crude oily product (2.50 g) was dissolved in a minimal amount of benzene and purified by rapid chromatography on basic alumina, activity IV, with 4% dioxane in cyclohexane as the eluant. Removal of the solvent under vacuum with avoidance of excessive heating, followed by trituration with pentane, afforded pure **1a** (2.28 g, 93%), mp 68–69 °C (lit.[8] mp 67–68 °C); the NMR spectrum was in essential agreement with that reported.[8] This workup procedure affords superior yields of pure **1a** than the methods described earlier.[7,8]

Pyrene-4-carboxaldehyde. To a solution of 4-bromopyrene (2.81 g, 10 mmol) in 200 mL of ether–THF (1:1) at −50 °C was added slowly *n*-butyllithium (15 mmol of 1.6 M in hexane) under N_2. The bright red solution was stirred at −50 °C for 2 h and then treated slowly with dry DMF (1.50 g, 20.5 mmol). Following the addition, the reaction mixture was stirred at −30 to −50 °C for 1 h and then at 20–25 °C for 15 h. Conventional workup followed by crystallization from CH_2Cl_2 furnished pure pyrene-4-carboxaldehyde (2.13 g, 93%): mp 161–162 °C; NMR δ 7.65–8.35 (m, 8, aromatic), 9.40 (apparent d, 1, H_3), 10.34 (s, 1, CHO).

4-Oxiranylpyrene (3). Reaction of pyrene-4-carboxaldehyde with dimethylsulfonium methylide by the procedure employed for **1a** provided pure **3** (2.19 g, 90%): mp 88–89 °C dec; NMR (500 MHz) δ 2.95 (dd, 1, CH_2), 3.42 (dd, 1, CH_2), 4.66 (dd, 1, CH), 7.97–8.22 (m, 8, aromatic), 8.42 (d, 1, H_3, $J_{2,3}$ = 8.1 Hz); mass spectrum, *m/e* 244; UV λ_{max}^{EtOH} 201 (ε 21 900), 231 (29 500), 240 (57 100), 262 (17 100), 273 (32 380), 307 (6700), 320 (19 000), 336 (29 500).

2-Acetyl-4,5,9,10-tetrahydropyrene (6a). A mixture of $AlCl_3$ (3.0 g, 22.5 mmol) and acetyl chloride (18 mL) was cooled to 0 °C, and a solution of **5** (2.06 g, 10 mmol) in CS_2 (70 mL) was gradually introduced. The reaction mixture was stirred at ambient temperature for 2 h, then poured on ice, and left to stir overnight. The solid was removed by filtration, washed with water, dried, and purified by chromatography on Florisil. Elution with 10% ether in benzene followed by recrystallization from benzene afforded pure **6a** (2.12 g, 86%): mp 113–114 °C; NMR δ 2.58 (s, 3, CH_3), 2.80 (s, 8, CH_2), 7.14 (s, 3, $H_{6,7,8}$), 7.72 (s, 2, $H_{1,3}$).

2-Acetylpyrene (7a). A solution of **6a** (1.24 g, 5 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (5.67 g, 10.5 mmol) in dry benzene (50 mL) was heated at reflux under N_2 for 20 h. The reaction mixture was cooled and filtered through diatomaceous earth to remove the reduced DDQ. Diethyl ether (200 mL) was added to the filtrate, and the solution was washed with 5% aqueous KOH and water and dried. Evaporation of the solvent followed by chromatography on Florisil with CH_2Cl_2 as the eluant gave **7a** (1.15 g, 93%): mp 145–146 °C (benzene–hexane) (lit.[9] mp 141–142 °C); NMR δ 2.74 (s, 3, CH_3), 7.73–8.15 (m, 7, aromatic), 8.43 (s, 1, $H_{1,3}$).

1-(1-Hydroxyethyl)pyrene (7b). Reduction of **7a** (1.00 g, 4.1 mmol) with $NaBH_4$ (2.00 g, 26.3 mmol) in anhydrous methanol (300 mL) for 2 h gave **7b** (1.00 g, 100%): mp 193–195 °C; NMR δ 1.66 (d, 3, CH_3), 2.18 (br s, 1, OH), 5.21 (q, 1, CH), 7.83–8.30 (m, 9, aromatic).

2-Vinylpyrene (7c). A solution of **7b** (500 mg, 2.0 mmol) and *p*-toluenesulfonic acid (50 mg) in dry benzene (500 mL) was refluxed for 20 h. The usual workup followed by chromatography on silica gel with hexane as the eluant afforded pure **7c** (360 mg, 79%): mp 89–90 °C; NMR δ 5.45 (dd, 1, CH_2), 6.08 (dd, 1, CH_2), 7.10 (dd, 1, CH), 7.90–8.30 (m, 9, aromatic). Attempted recrystallization of **7c** resulted in partial decomposition and/or polymerization.

2-Oxiranylpyrene (2a). A solution of **7c** (100 mg, 0.44 mmol) and *m*-chloroperbenzoic acid (760 mg, 4.4 mmol) in THF (20 mL) was stirred under N_2 for 5 h. At that time, TLC on silica gel

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indicated the presence of unreacted olefin. Nevertheless, reaction was quenched to minimize the likelihood of product decomposition. The product was partitioned between ether and water. The organic layer was washed with water, dried, and evaporated under reduced pressure avoiding excessive heating. Chromatography on neutral alumina, activity IV, gave unreacted **7c** (30 mg, 30%) on initial elution with hexanes. Elution with benzene afforded pure **2a** (65 mg, 63%): mp 127–128 °C dec; NMR δ 2.94 (dd, 1, CH_2), 3.31 (dd, 1, CH_2), 4.27 (br t, 1, CH), 7.80–8.30 (m, 9, aromatic); mass spectrum, *m/e* 244.

2,7-Diacetyl-4,5,9,10-tetrahydropyrene (6b). Acetylation of **5** (1.0 g, 5 mmol) was conducted by the procedure previously employed with replacement of CS_2 by CH_2Cl_2 as solvent. There was obtained **6b** (1.42 g, 98%): mp 225–227 °C (benzene–hexane); NMR δ 2.63 (s, 6, CH_3), 2.97 (s, 8, CH_2), 7.80 (s, 4, aromatic).

2,7-Diacetylpyrene (7d). Dehydrogenation of **6b** (1.45 g, 5 mmol) was carried out by the procedure employed for the monoacetyl compound, except that 3 days were required for complete reaction. There was obtained **7d** (1.40 g, 98%): mp >265 °C (CH_2Cl_2); NMR δ 2.96 (s, 6, CH_3), 8.24 (s, 4, $H_{4,5,9,10}$), 9.84 (br s, 4, $H_{1,3,6,8}$).

2,7-Bis(1-hydroxyethyl)pyrene (7e). Reduction of **7d** (1.00 g, 3.5 mmol) with $NaBH_4$ by the procedure employed for 2-acetylpyrene gave **7e** (1.00 g, 98%): mp >250 °C; NMR δ 1.69 (d, 6, CH_3), 2.35 (br s, 2, OH), 5.33 (q, 2, CH), 7.92 (s, 4, $H_{4,5,9,10}$), 8.10 (s, 4, $H_{1,3,6,8}$).

2,7-Divinylpyrene (7f). Dehydration of **7e** (1.45 g, 5 mmol) by the procedure employed for **7b** furnished 2,7-divinylpyrene (1.0 g, 79%): mp 177–178 °C; NMR δ 5.44 (d, 2, CH_2), 6.05 (d, 2, CH_2), 7.13 (dd, 2, CH), 8.00 (s, 4, $H_{4,5,9,10}$), 8.18 (s, 4, $H_{1,3,6,8}$).

2,7-Bisoxiranylpyrene (2b). A mixture of **7f** (100 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) and phosphate buffer (5 mL, pH 8.0) was cooled to 4 °C and *m*-chloroperbenzoic acid (68 mg, 0.39 mmol) was added with stirring. TLC analysis indicated reaction was incomplete after 3 days at 4 °C. Another portion (68 mg) of the peracid was added and stirring was continued for 5 days, when a final portion (68 mg) of peracid was added. The mixture was stirred at 4 °C for 7 days more and then diethyl ether (50 mL) was added. The aqueous layer was removed, and the organic layer was washed with ice-cold 2% NaOH solution (2 × 50 mL) and distilled water (2 × 20 mL) and dried (Na_2SO_4). The solution was filtered and the solvent removed under reduced pressure (no heat). The residue was purified by rapid chromatography on a column of basic alumina, activity IV, eluted with 20% benzene in hexane. Evaporation of the solvent gave **2b** (81 mg, 73%): mp 145–147 °C dec; NMR δ 3.00 (dd, 2, CH_2, J = 3.1 Hz), 3.30 (dd, 2, CH_2, J = 4.9 Hz), 4.32 (apparent t, 2, CH, J = 4.3 Hz), 8.13 (s, 4, aromatic $H_{4,5,9,10}$), 8.26 (s, 4, aromatic $H_{1,3,6,8}$); mass spectrum, *m/e* 286.

1,6- and 1,8-Bis(bromoacetyl)pyrene (8b and 9b). A solution of 1,6-diacetylpyrene[16] (1.43 g, 5 mmol) in EtOAc (20 mL) and $CHCl_3$ (20 mL) was heated to reflux with 4.69 g (20 mmol) of finely powdered $CuBr_2$ with vigorous stirring for 3.5 h. The yellow precipitate was filtered off, washed with CH_2Cl_2, dried, and combined with the residue obtained from evaporation of the filtrate. This material (5.28 g) was extracted with boiling benzene (5 × 125 mL), filtered, and concentrated. Crystallization gave **8b** (908 mg, 41%): mp 169.5–171 °C dec; NMR δ 8.29–9.07 (m, 8, aromatic), 4.71 (s, 4, CH_2). Analogous reaction of 1,8-diacetylpyrene[16] (1.15 g, 4 mmol) afforded **9b** (1.40 g, 79%), as yellow crystals: mp 194.5–195.5 °C dec; NMR (Me_2SO-d_6) δ 4.70 (s, 4, CH_2), 8.19 (s, 2, $H_{4,5}$), 8.27 (d, 2, $H_{3,6}$), 8.40 (d, 2, $H_{2,7}$), 9.00 (s, 2, $H_{9,10}$, $J_{2,3}$ = 8.0 Hz); UV λ_{max}^{EtOH} 204 (ϵ 35 200), 232 (46 900), 243 (40 500), 288 (27 700), 377 (27 700).

1,6- and 1,8-Bisoxiranylpyrene (1b and 1c). To a stirred suspension of **8b** (444 mg, 1 mmol) in boiling EtOH (20 mL) was added dropwise a solution of $NaBH_4$ (112 mg, 3 mmol) in 2 mL of H_2O. The mixture was refluxed for 5 min and filtered hot. The filtrate was cooled at 4 °C for 30 min, and the crystalline precipitate filtered to give **1b** (72 mg), mp 158–159 °C dec. The insoluble material from the reaction was triturated with H_2O, and the yellow crystals were filtered off, washed with H_2O and MeOH, and dried to yield **1b** (113 mg, total yield with previous crop 65%): mp 187–190 °C dec; NMR δ 2.97 (m, 2, CH_2), 3.41 (dd, 2, CH_2), 4.75 (dd, 2, CH), 7.98 (d, 2, $H_{3,8}$), 8.12 (d, 2, $H_{4,9}$), 8.17 (d, 2, $H_{2,7}$), 8.37 (d, 2, $H_{5,10}$, $J_{4,5}$ = 9.2 Hz, $J_{2,3}$ = 7.8 Hz); UV spectrum λ_{max}^{EtOH} 201 (ϵ 23 600), 233 (32 300), 242 (58 400), 256 (s, 7450), 266 (22 360), 277 (44 700), 317 (9940), 332 (27 950), 349 (41 600). Analogous reaction of **9b** (444 mg, 1 mmol) provided **1c** (191 mg, 67%): mp 142–144 °C; NMR (500 MHz) δ 2.97 (m, 2, CH_2), 3.44 (dd, 2, CH_2), 4.79 (apparent t, 2, CH), 7.97 (d, 2, $H_{3,6}$), 8.03 (s, 2, $H_{4,5}$), 8.16 (d, 2, $H_{2,7}$), 8.47 (s, 2, $H_{9,10}$, $J_{2,3}$ = 8.0 Hz); UV spectrum λ_{max}^{EtOH} 202 (ϵ 33 800), 234 (44 200), 242 (69 300), 256 (s, 13 900), 266 (28 600), 277 (51 100), 304 (s, 6100), 318 (13 000), 333 (31 600), 349 (43 300).

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Registry No. **1a**, 61695-74-7; **1b**, 86470-94-2; **1c**, 86470-95-3; **2a**, 86470-96-4; **2b**, 86470-97-5; **3**, 73529-24-5; **5**, 781-17-9; **6a**, 82799-67-5; **6b**, 86470-98-6; **7a**, 789-06-0; **7b**, 86470-99-7; **7c**, 86471-00-3; **7d**, 86471-01-4; **7e**, 86471-02-5; **7f**, 86471-03-6; **8a**, 86471-04-7; **8b**, 86471-05-8; **9a**, 86471-06-9; **9b**, 86471-07-0; DMF, 68-12-2; 4,5-dihydropyrene, 6628-98-4; pyrene-1-carboxaldehyde, 3029-19-4; dimethylsulfonium methylide, 6814-64-8; trimethylsulfonium iodide, 2181-42-2; 4-bromopyrene, 1732-26-9; pyrene-4-carboxaldehyde, 22245-51-8; acetyl chloride, 75-36-5.

A Simple, Inexpensive Procedure for the Large-Scale Production of Alkyl Quinones

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Alkyl *p*-benzoquinones are versatile starting materials in the synthesis of many important natural products and are particularly useful as dienophiles in Diels–Alder reactions. Quinones may be produced in high yield through the exposure of *o*-arylhydroxylamines to strong acid or by the oxidation of phenols and aromatic amines with (inter alia) Fremy's salt[2] or thallium(III) nitrate.[3] Unfortunately, each of these methods suffers certain disadvantages. For example, since *o*-arylhydroxylamines are usually prepared by reduction of their corresponding nitro compounds, they are oftentimes produced in low yield and are heavily contaminated with nitroso, amino, azo, and azoxy byproducts. As a consequence, many *o*-arylhydroxylamines are not always readily available as starting materials.

On the other hand, aromatic amines and phenols are readily available and are usually quite inexpensive to purchase. However, the two best reagents for the oxidation of these substrates (i.e., Fremy's salt and thallium(III) nitrate) are relatively expensive reagents. Moreover, although both reagents are effective oxidants, the former exhibits explosive properties, and the latter produces highly toxic byproducts. While these features are certainly quite manageable in small-scale reactions, they have proven to be particularly bothersome to us in large-scale quinone production.

We report herein a simple method for the large-scale production of alkyl quinones which does not suffer from any of the disadvantages discussed above. The method

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